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Title: "How long have I got?" – a prospective cohort study comparing validated prognostic factors for use in patients with advanced cancer.

Running Head: prognostic biomarkers in advanced cancer

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Key words: prognosis; inflammation; survival; cancer; palliative

Abstract

Background

The optimal prognostic factors in patients with advanced cancer are not known as a comparison of these is lacking. The aim of the present study was to determine the optimal prognostic factors by comparing ~~the most~~ validated factors.

Materials and Methods

A multicentre, prospective observational cohort study recruited patients over 18 years with advanced cancer. The following were assessed: clinician predicted survival (CPS), Eastern Cooperative Oncology Group performance status (ECOG – PS), patient reported outcome measures (anorexia, cognitive impairment, dyspnoea, global health), metastatic disease, weight loss, modified Glasgow Prognostic Score (mGPS) based on C-reactive protein (CRP) and albumin, lactate dehydrogenase (LDH), and white (WCC), neutrophil (NC) and lymphocyte (LCC) cell counts. Survival at one and three months was assessed using area under the receiver operating curve (AUC) and logistic regression analysis.

Results

Data were available on 478 patients and the median (IQR) survival was 4.27 (1.86-7.03) months. On univariate analysis, the following factors predicted death at one and three months: CPS, ECOG-PS, mGPS, WCC, NC (all $p<0.001$), dyspnoea, global health (both $p\leq0.001$), cognitive impairment, anorexia, LDH (all $p<0.01$) and weight loss ($p<0.05$). On multivariate analysis ECOG-PS, mGPS and NC were independent predictors of survival at one and three months (all $p<0.01$).

Conclusions

The simple combination of ECOG-PS and mGPS is an important novel prognostic framework which can alert clinicians to patients with good performance status who are at increased risk of having a higher symptom burden and dying at 3 months. From the recent

literature it is likely that this framework will also be useful in referral for early palliative care with 6-24 months survival.

Key words: prognosis; inflammation; survival; cancer; palliative

Implications for practice.

- This large cohort study examined all validated prognostic factors in a head-to-head comparison and demonstrate the superior prognostic value of the ECOG-PS/mGPS combination over other prognostic factors.
- This combination is simple, accurate and also relates to quality of life. It may be useful in identifying patients who may benefit from early referral to palliative care.
- We propose ECOG-Performance Status/mGPS as the new prognostic domain in patients with advanced cancer.

Gap between current and best practice

- ECOG-PS is currently used as the main prognostic marker however it can be challenging to accurately assess and is subjective.
- The systemic inflammatory response as measured by the modified Glasgow Prognostic Score (mGPS), has been extensively reported and is comparable to PS in terms of prognostic accuracy; however the mGPS is entirely objective.
- The best practice in prognostication would be to use the combination of ECOG-PS/mGPS which improves survival prediction of either in isolation.

Learning Objectives

BEST PRACTICE	CURRENT PRACTICE	RESULTING GAPS	LEARNING OBJECTIVES
ECOG-PS and mGPS in combination work better than either in isolation and reliably predicts survival in patients with advanced cancer.	ECOG-PS is the main prognostic marker used in patients with advanced cancer.	The use of the ECOG-PS/ mGPS framework requires to be evaluated in the context of randomised controlled trials in clinical oncology.	To understand that various clinic-pathological factors are prognostic. To understand that the ECOG-PS/mGPS framework reliably predicts survival in patients with advanced cancer. To be aware that ECOG-PS/mGPS framework relates to quality of life.

Background

"How long have I got?"

This is often the first question patients ask when they are told that their cancer is incurable. Most clinicians find this challenging to answer but rely on their experience, clinical intuition and the possible outcome of therapies, when considering their answer. Of course, some patients may not want to know their likely outcome. Either way, it is important that the clinician has an awareness of the likely survival as this will inform important decisions around appropriateness of anti-cancer therapy[1, 2] and place of care.[3] It may also relieve patient and family anxiety associated with prognostic uncertainty.[3]

In patients with advanced cancer, measures of performance status (e.g. Eastern Cooperative Oncology Group Performance Status [ECOG-PS]) remain the most reliable prognostic factor. These are widely used in oncology practice to help inform important decisions but have been criticised as being subjective, inaccurate and overly optimistic. [4]

Since 2005, there has been a clear drive to try and augment prognostic accuracy with several clinical and bio-markers being identified as having prognostic value.[5-7] Clinical markers with prognostic value include anorexia, cognitive impairment, dyspnoea, global health and weight loss in the last 3 months.[5, 8] Bio-markers include lactate dehydrogenase (LDH), and white (WCC), neutrophil (NC) and lymphocyte (LC) cell counts, and the modified Glasgow Prognostic Score (mGPS – a combination of C-reactive protein [CRP] and Albumin). The mGPS measures the inflammatory response and has demonstrated the role of the host-tumour inflammatory response in prognosis[9] in addition to its established role in tumour genesis and quality of life.[10, 11]

Although such factors have been identified and advocated, it is not clear which factors are optimal since a comparison has not, to date, been done. ~~Despite the time invested in advancing the research agenda in prognosis, it is not clear what the optimal prognostic~~

~~factors are as a prospective comparison has not been done.~~ In particular, it is not known how established prognostic markers such as performance status compare to newer clinical and bio-markers. Therefore, the aim of the present study was to compare prospectively, validated prognostic factors in a cohort of patients with advanced cancer.

Methods

Study Population

Adult patients (≥ 18 years) were recruited from either one of nine regional cancer centre's or one of seven specialist palliative care units in the UK (listed in acknowledgements). Patients had cancer which was defined as incurable. This encompassed metastatic cancer [histological, cytological or radiological evidence], non-disseminated cancer (e.g. glioblastoma multiforme), locally advanced cancer (e.g. pancreatic cancer) or haematological malignancies who were being treated/previously been treated with anti-cancer therapy with palliative intent. Eligible patients also were able to complete study questionnaires; provide a venous blood sample; performance status of 1-4 (ECOG) as agreed by their treating clinician. Patients were excluded if they had breast or prostate carcinoma with only bone metastases, as in some cases their survival may be many years. Patients were either inpatients or outpatients, undergoing anti-cancer therapy or not. Adjustments were made for age, sex and having lung, gastrointestinal or other cancers and the analysis adjusted accordingly. There were no protocol modifications. The study had ethics committee approval (UK – 12/SS/0181) and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The study adhered to the STROBE guidelines for cohort studies.

Centres were opened on a staggered basis. At each centre, consecutive patients who met the eligibility criteria were invited to participate (sequential sampling) and consented, reducing selection bias. All assessments, including blood sampling, were done on the day of consent.

Prognostic markers

Patient's age, sex, and demographics were recorded, as were details of underlying disease including metastases. The prognostic tools/factors examined in the present

prospective study were those previously identified from a systematic review undertaken by our group.).[6] In brief, these prognostic tools/factors had been validated in adult patients with advanced cancer (n>100).

Clinical markers: Clinician Predicted Survival (CPS) and ECOG-PS, the presence of metastases and weight loss (in the previous 3 months) were assessed by the treating clinician. The patient reported outcome measures (PROMs) dyspnoea, global health, cognitive impairment and anorexia were assessed by the patient using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30).[12]

Bio-markers: CRP and albumin (combined in the mGPS), LDH, WCC, NC and LC.

Statistical Analysis

The primary outcome was to compare the prognostic value of the aforementioned factors. The secondary outcomes were to assess if such factors had independent prognostic value and could be combined to improve prediction of survival at one and three months from study entry. These time points were chosen as clinically relevant for the management of patients with advanced cancer.[6, 13, 14]

The primary outcome was to compare the prognostic value of the aforementioned factors on survival at one and three months using the area under the receiver operator curve method. The sample size was based on a systematic review to identify key prognostic markers in patients with advanced cancer.[6] Based on this information a sample size of approximately 500 patients would have the power to reliably assess the prognostic value of approximately 10 variables.[15]

The following were grouped according to specific thresholds. The mGPS was grouped as: CRP $\leq$10 mg/L = 0, CRP >10 mg/L = 1, CRP >10 mg/L and albumin < 35 g/L = 2.[16] Weight loss was grouped: <2.5%, 2.5-5.9%, 6-10.9%, 11-14.9, >15% according to

thresholds described by Martin et al.[17] WCC, NC and LC were categorised as above or below/equal to normal limits.[18] LDH was classified as abnormal if >250 U/L.[19] EORTC QLQ-C30 scores were calculated using scoring procedures as described by Aaronson et al.[12] EORTC QLQ-C30 scales were analyzed as discrete categories representing underlying continuous constructs and PROMs (symptoms and quality of life variables) were defined as being present if the score was greater than 50.[20] CPS was categorised into days [≤14days], weeks [15-56 days] or months [≥57 days]). For categorical variables with >2 categories (e.g. mGPS, ECOG-PS, weight loss, CPS), these were treated as continuous variables in terms of Hazard Ratios in line with their proven prognostic value. [10]

All patients were followed up until death or study censoring which was the date of the end of the study (3.7.15) and nine months after the last patient was recruited. The survival time was defined as the number of months from study entry until death, or censored if patients were alive at follow-up date. Area under the receiver operating curve (AUC) was measured to assess survival at one and three months. Univariate logistic regression was used to examine whether the prognostic factors were predictive of death at one month and three months post consent. Multivariate survival analysis was done using a stepwise backward conditional procedure to derive a final model of prognostic factors that had a significant independent relationship with survival at one month and three months. Only variables with a univariate $p<0.1$ were considered in the model.

To examine the relationship between ECOG-PS, mGPS and quality of life a series of X^2 tests for trend were used. Quality of life was calculated using the summary score of the EORTC QLQ-C30 with a maximum score of 100.[21]

All statistical testing was done at the 5% significance level with 95% confidence intervals reported. In order to adjust for multiple comparisons in the present study a p value of <0.01 was considered significant. All analyses were performed using IBM SPSS Version 23.0 (SPSS, Chicago, IL). Where appropriate, mean and standard deviations (SD) or median

and inter-quartile range (IQR) are reported. Patients who have missing survival time end point (i.e. last known date alive or date of death) are not included in the analyses.

The study design was developed in conjunction with lay members of the National Cancer Research Institute palliative care clinical studies development group, including cancer survivors.

Results

Between 24th January 2013 and 25th September 2014, 563 were screened with 539 recruited and core data available on ECOG-PS available on 478 (88.7%). The clinicopathological characteristics of patients are shown in Table 1. The mean (SD) age was 67.04 (12.08) years and 256 (54%) patients were female. The minimum and median (IQR) follow up for survivors was 0 days and 198 (137-273) days respectively. When study data collection stopped, 194 (41%) patients were alive. The median (IQR) survival was 4.27 (1.86-7.03) months. The most common cancer type was lung present in 177 (37%) patients and metastases were present in 377 (85%) patients.

The relationship between clinical- and bio-markers and survival at one and three months, using the AUC is shown in Table 2. ECOG-PS and mGPS had the highest AUC for survival at one month: ECOG-PS 0.79 (95% CI, 0.73-0.85; p<0.001) and mGPS 0.73 (95% CI, 0.67-0.79; p<0.001). ECOG-PS and mGPS had the highest AUC for survival at three months: ECOG-PS 0.79 (95% CI, 0.71-0.81; p<0.001) and mGPS 0.74 (95% CI, 0.70-0.79; p<0.001).

The univariate and multivariate analysis of survival at one and three months is shown in Table 3. The following independently predicted death at one month: ECOG-PS (HR 2.15, 95%CI 1.40-3.30, p<0.001), mGPS (HR 2.03, 95%CI 1.23-3.35, p=0.006), and NC (HR 3.18, 95%CI 1.67-6.01), p<0.001). The following independently predicted death at three months: ECOG-PS (HR 1.91, 95%CI 1.47-2.49, p<0.001), mGPS (HR 1.77, 95%CI 1.36-2.31,

p<0.001), weight loss (HR, 1.15, 95%CI 1.03-1.29, p=0.013), LDH (HR 2.00, 95%CI 1.15-3.47, p=0.013) and WCC (HR 2.50, 95%CI 1.71-3.66, p<0.001).

The percentage survival (SE) at one and three months as per the factors which are the strongest predictors of survival on multivariate analysis, is shown in Table 4. To illustrate, survival at one month ranges from 98(1)% ECOG-PS1 to 25(11)% ECOG-PS 4. It is of note that the factors with the greatest discrimination in survival at one and three months are ECOG-PS and the mGPS.

The relationship between ECOG-PS, mGPS and quality of life was also examined (data not shown). Decreasing PS and increasing inflammation were independently associated with deteriorating quality of life. In combination mean quality of life scores ranged from 80 (ECOG-PS1, mGPS 0) to 46 (ECOG-PS3, mGPS 2) p<0.001; the combination providing a greater differentiation of quality of life scores than each component in isolation (ECOG-PS or mGPS) in isolation.

Discussion

A number of clinical and bio-markers predict survival one and three month survival in patients with advanced cancer. The present study compares these prospectively and shows the superior prognostic value of several key prognostic factors including performance status and biomarkers of the inflammatory response (e.g. mGPS). It is of interest that markers of the inflammatory response compare favourably to performance status in terms of survival prediction. In the present study the prognostic value of ECOG-PS and mGPS was retained when adjusted for age, sex and cancer location. Given that both ECOG-PS and mGPS have been extensively validated in both observational and randomised clinical trial settings it is likely that this prognostic framework will be clinically useful in the majority of common solid tumours. ~~Further, ECOG-PS and mGPS predicts survival but are also related to overall quality of life.~~

The results of the present study should reassure clinicians of the value of performance status in prognostication. However the findings should also alert clinicians that patients who have a good performance status and systemic inflammation are at increased risk of poorer quality of life and survival. ~~but also have a higher symptom burden.~~ The ECOG-PS/mGPS framework reported herein has been validated previously by our group and could be used to stratify patients who may benefit from referral to palliative care services.[11, 13]

~~The present study advances the research agenda in the area of prognostication~~. In patients with advanced cancer, the decision is often not "can we treat with anti-cancer therapy?" rather "should we treat with anti-cancer therapy?", and accurate assessment of prognosis is a key consideration in this regard. Using robust prognostic factors (e.g. biomarkers of the inflammatory response) in combination with clinical judgement, may help inform decisions regarding appropriate place for end of life care (e.g. hospice admission), while the latter may inform the decision to continue with anti-cancer therapy (e.g. radiotherapy for painful bone metastases) or clinical trial participation.

To our knowledge, this is the first report to prospectively compare validated prognostic factors for use in patients with advanced cancer. It was of interest that a number of validated prognostic factors did not, on multivariate analysis, retain independent prognostic value at one and three months. For example weight loss was less prominent as an independent prognostic factor than might be anticipated from the literature pertaining to the cachexia associated with cancer. Indeed, the prominence of weight loss as the cornerstone of palliation in patients with advanced cancer has been questioned.[22-24] Further, PROMs often associated with reduced survival (dyspnoea, global health, cognitive impairment and anorexia) were less prominent suggesting that their prognostic value is dependent at least in part, on physical function and the systemic inflammatory response. Indeed, significant associations have been reported between such PROMs, physical function and systemic inflammation in large independent cohorts.[8, 11] If this were to be the case, then

improvement in physical function[25] and moderation of the systemic inflammatory response[26] should result in an improvement of such PROMs.

This would be in keeping with observations that the systemic inflammatory response has prognostic value in non-malignant conditions with recent work supporting the inflammatory hypothesis of atherosclerosis.[27] Although in cancer the use of anti-inflammatory therapies in a tumouricidal role is increasing, the sound argument of targeting the inflammatory response to influence survival in cancer, has by in large been neglected. The results from the present study support the hypothesis that the inflammatory response is a key driving factor in survival in cancer and the need for an increased recognition its importance as a therapeutic target for palliation in patients with advanced cancer.[11, 28]

Recently, a number of groups have carried out a prospective comparison of validated prognostic factors in patients in the palliative care setting. For example, Baba and co-workers reported, in approximately 2,500 patients in a multicentre study in variety of palliative care settings, the feasibility and accuracy of the PaP score, D-PaP score, PPI and modified PiPS model, including patients receiving chemotherapy.[7] The most important finding was that all prediction tools investigated in the study, PaP score, D-PaP score, PPI and modified PiPS model, can differentiate subgroups with different survival profiles in all palliative care settings. Similarly, Hui and co-workers reported, in approximately 200 patients with advanced cancer, that PaP-score was more accurate than CPS, and the addition of CPS to the prognostic model reduced its accuracy.[29]

Therefore, it is clear that the prognostic models PPI and PaP have indeed reliable prognostic value. However, these prognostic models include ECOG-PS and the PaP also includes CPS. Indeed, the prognostic value of these models depend largely on the assessment of functional status as a core component and ECOG-PS, compared with the sparse use of PPI and PaP tools, is used extensively in routine clinical practice.[6] (Simmons et al., 2017). Therefore, in addition to ECOG-PS, a number of core prognostic variables that were

identified in a recent systematic review, including the mGPS, were included in the present analysis.[6] This approach has the advantage of identifying core prognostic variables that add substantially to ECOG-PS and thereby simplifying the patient assessment.

In the present study after ECOG-PS and mGPS, CPS was the third and fourth most significant factor predicting death at one- and three months, respectively. Although due to its subjective nature CPS is often reported as being inaccurate, the present results confirm the clinical utility of the CPS. In the context of the integration of palliative care and oncology the combination of CPS and either ECOG-PS or mGPS was not examined in the present study

The primary outcome was a direct comparison of variables previously identified to have prognostic value in patients with advanced cancer. It was clear from the present analysis that a number of prognostic variables had AUC with overlapping 95% CI. This perhaps not surprising since for example performance status is a key component of the CPS and a number of prognostic tools in patients with advanced cancer.[6] With the increasing integration of oncology and palliative care [30] it is likely that performance status will increasingly form the cornerstone of outcome prediction.

Limitations

The present study had a number of limitations. As the majority of patients were under the care of palliative care services, it may be assumed they had a high symptom burden, which itself may be an indicator of a shorter prognosis. Further, although recruitment was across 16 centres, the present cohort may not be entirely representative, but was well defined in terms of the components of validated prognostic scores. This will allow comparison with other populations in future studies. ~~Another limitation was that not all reported prognostic factors were evaluated. However, the choice of factors was based on a rigorous systematic review and only those which were assessed in populations greater than 100, and examined and validated in two or more independent data sets, were included.~~ Another limitation is that

the recruitment/sampling strategy was opportunistic however the heterogeneity of the primary cancer types herein would support the findings in multiple tumour types. Patients with delirium based on clinical assessment were not included in the present study. However, formal screening for delirium was not carried out as part of eligibility assessment and it is possible that patients with hypoactive delirium were not identified and therefore may have been recruited as part of the study. In the present study the EORTC-QLQ-30 was used to assess symptoms and cognitive impairment. Although this has been used and validated extensively there are now more targeted and sensitive tools available. Further studies are required to examine whether such tools enhance the ECOG-PS/ mGPS framework.

Another limitation of the present study is that some of the variables studied (e.g. symptoms) were dichotomised based on 50% since the ideal cut-off was not clear from the literature. This was a pragmatic approach to examine whether the variable had prognostic value.

The median survival of the studied population was 4 months and therefore the efficacy of the ECOG-PS/mGPS framework may not be useful in other cohorts of patients with advanced care that have a different survival profile. However, given the simplicity and objective nature of the framework it is likely that it will tested extensively in different patient cohorts.[31]

~~Clearly assessment of performance status is subjective, however this is probably in keeping with day-to-day clinical practice. Although it is widely recognised that ECOG-PS is a subjective measure and has questionable inter-rater reliability, the value of PS as a key prognostic marker in advanced cancer is well recognised.[32]~~

Conclusion

In the first prospective comparison of validated prognostic factors, most factors predicted survival; however the superior value of performance status and biomarkers of the

inflammatory response (mGPS, neutrophil count) were demonstrated. Moreover, combining clinical factors with biomarkers (e.g. performance status with the mGPS) has been reported to have a differential impact on quality of life.[11, 13] This framework should alert clinicians to patients who are at increased risk of dying, but may also have a higher symptom burden.

Authors Contributions

BL, DM, KF and MF led the development of the work. BL and DM prepared the draft manuscript and led the writing. ST and CG provided statistical support. BL and MF were the principal investigators for the study and CS oversaw the data collection. AW, MB, AMcK, CO and CU provided significant intellectual input and advice in the re-draft of the manuscript. All authors approved the final version of the manuscript.

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Disclosure of Potential Conflicts of Interest

None

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Table 1. Clinicopathological characteristics of patients with advanced cancer (n=478)

Parameter	n (%)
Age (≤65, 65-74, ≥74)	191(40), 140(29), 147(31)
Female	256 (54)
Place of care	
Home	341(71)
Hospital	30 (6)
Specialist Palliative Care Unit	93 (19)
Other	14 (3)
Primary Cancer	
Neurological	8 (2)
Lung	177 (37)
Gastrointestinal	141 (29)
Urological	24 (5)
Gynaecological	24 (5)
Melanoma	28 (6)
Haematological	10 (2)
Breast	50 (11)
Unknown Primary	8 (2)
Other	8 (2)
Previous Anti-cancer therapy	
Chemotherapy	281/478 (59)
Radiotherapy	187/478 (39)
Hormonal	42/478 (9)
Clinician Predicted Survival (n=463)	
Days	8/463 (2)
Weeks	87/463 (19)
Months	368/463 (79)
Performance Status (ECOG)	
1, 2, 3, 4	189(39), 201(42), 72(15), 16(3)
mGPS	
0, 1, 2	178 (37), 99(21), 201(42)
Patient Reported Outcome Measures [EORTC score, median (IQR)]	
Dyspnoea present	139/461 (30); [33 (0-67)]
Global Health impaired	217/459 (47); [83 (50-100)]
Cognitive impairment	331/461 (72); [83 (50-100)]
Anorexia	159/461 (34); [33 (0-67)]
Metastases present	377/446 (85)
Weight loss last 3 months (%) (n=462)	
<2.5, 2.5-5.9, 6-10.9,11-14.9, >15	272(59),31(7),60(13),42(9),57(12)
Biomarkers [median (IQR)]	
Elevated LDH (>250 U/L)	335/446 (75%); [394 (251-557)]
Elevated White Cell Count (>11 $x10^9$/L)	124/470 (26%); [7.7 (5.6-11.4)]
Elevated Neutrophil Count >7.5 x 10^9/L	148/469 (32%); [5.2 (3.5-8.8)]
Elevated Lymphocyte Count 3.0 $x10^9$/L	20/469 (4%); [1.2 (0.8-1.70)]

Table 2 - The relationship between prognostic factors and survival (one month and three months) in patients with advanced cancer.

	Death at one month			Death at 3 months		
	%	AUC (95% CI)	P	%	AUC (95% CI)	P
Age (<65/65-74/>74)	13/13/18	0.57 (0.49-0.66)	0.044	28/39/37	0.56 (0.50-0.62)	0.048
Sex (male/ female)	16/13	0.47 (0.38-0.55)	0.044	39/31	0.44 (0.40-0.50)	0.054
Clinician Predicted Survival						
Months/Weeks/Days	8/37/100	0.71 (0.63-0.79)	<0.001	25/72/100	0.68 (0.62 -0.73)	<0.001
Performance Status (ECOG)						
1/2/3/4	2/13/38/75	0.79 (0.73-0.85)	<0.001	13/37/71/94	0.79 (0.71- 0.81)	<0.001
Patient Reported Outcome Measures						
Dyspnoea (N/Y)	10/22	0.61 (0.53-0.69)	0.005	26/49	0.61 (0.56-0.67)	<0.001
Global Health (Y/N)	8/19	0.61 (0.54-0.69)	0.005	24/43	0.61 (0.55-0.66)	<0.001
Cognitive Impairment (N/Y)	21/10	0.41 (0.33-0.49)	0.019	42/29	0.44 (0.38-0.49)	0.03
Anorexia (N/Y)	10/20	0.59 (0.52-0.68)	0.014	26/46	0.60 (0.54-0.66)	0.001
Metastases (N/Y)	10/15	0.55 (0.46-0.63)	0.041	33/36	0.51 (0.45-0.57)	0.78
Weight loss last 3 months (%)						
<2.5/2.5-5.9/6-10.9/11-14.9/>15	13/3/10/7/32	0.56 (0.47-0.66)	0.14		0.62 (0.55-0.67)	<0.001
Biomarkers						
mGPS 0/1/2	2/14/26	0.73 (0.67-0.79)	<0.001	9/38/55	0.74 (0.70-0.79)	<0.001
LDH <=250/>250 U/L	5/18	0.59 (0.51-0.66)	0.039	15/40	0.61 (0.55-0.66)	0.001
White Cell Count <=11/>11 x10^9/L	7/33	0.68 (0.60-0.77)	<0.001	24/60	0.64 (0.58-0.70)	<0.001
Neutrophil Count <=7.5/ >7.5 x	7/29	0.72 (0.64-0.80)	<0.001	23/57	0.67 (0.61-0.73)	<0.001
Lymphocyte Count <=3.0/>3.0	14/10	0.49 (0.40-0.57)	0.76	35/15	0.48 (0.42-0.54)	0.51

AUC- Area under the Receiver Operating Curve

Table 3. The relationship between prognostic factors and survival (one and three months) in patients with advanced cancer: univariate and multivariate analysis.

	Death at one month				Death at three months			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (≤65/65-74/≥74)	1.23 (0.92-1.63)	0.158			**1.19 (1.00-1.43)**	**0.056**		
Sex (male/ female)	0.78 (0.49-1.26)	0.309			**0.76 (0.56-1.04)**	**0.084**	0.59 (0.41-0.86)	0.006
Clinician Predicted Survival								
Months/Weeks/Days	**0.85 (0.78-0.90)**	**<0.001**			**0.80 (0.74-0.85)**	**<0.001**	0.35 (0.01-0.58)	0.047
Performance Status (ECOG)								
1/2/3/4	**3.71 (2.84 -**	**<0.001**	2.15 (1.40-3.30)	<0.001	**2.90 (2.42-3.47)**	**<0.001**	1.96 (1.50 -257)	<0.001
Patient Reported Outcome Measures								
Dyspnoea (N/Y)	**2.32 (1.41-3.82)**	**0.001**			**2.26 (1.64-3.11)**	**<0.001**		
Global Health (Y/N	**0.60 (0.31-0.73)**	**0.001**			**0.54 (0.36-0.67)**	**<0.001**		
Cognitive Impairment (N/Y)	**0.45 (0.27-0.75)**	**0.002**			**0.61 (0.44-0.85)**	**0.003**		
Anorexia (N/Y)	**2.21 (1.34-3.63)**	**0.002**			**2.09 (1.52-2.88)**	**<0.001**		
Metastases (N/Y)	1.57 (0.72-3.45)	0.379			1.14 (0.73-1.77)	0.564		
Weight loss last 3 months (%)								
<2.5/2.5-5.9/6-10.9/11-14.9/>15	**1.21(1.04-1.41)**	**0.017**			**1.26 (1.14-1.39)**	**<0.001**	1.16 (1.03-1.30)	0.012
Biomarkers								
mGPS 0/1/2	**3.15 (2.13-4.65)**	**<0.001**	2.03 (1.23-3.35)	0.006	**2.57 (2.08-3.19)**	**<0.001**	1.79 (1.37-2.33)	<0.001
LDH <=250/>250 U/L	**3.50 (1.51-8.11)**	**0.003**			**3.09 (1.86-5.11)**	**<0.001**	2.30 (1.32-4.01)	0.003
White Cell Count <=11/>11 x10^9/L	**5.53 (3.24-8.76)**	**<0.001**			**3.54 (2.59-4.84)**	**<0.001**		
Neutrophil Count <=7.5/ >7.5 x 10^9/L	**5.23 (3.12-8.56)**	**<0.001**	3.18 (1.67-6.01)	<0.001	**3.45 (2.52-4.72)**	**<0.001**	2.67 (1.83-3.93)	<0.001
Lymphocyte Count <=3.0/>3.0 x10^9/L	0.71 (0.18-2.88)	0.627			0.39 (0.13-1.29)	0.111		

Prognostic factors in bold used in multivariate analysis.

Table 4 – Percentage Survival (SE) at one and three months as per Clinician Predicted Survival, ECOG-Performance Status, modified Glasgow Prognostic Score, Lactate Dehydrogenase and Neutrophil Count categories.

		Survival	
		One month	Three months
Clinician Predicted Survival (n=463)	Days	n=8	n=8
	Weeks	63 (5) n=87	29 (5) n=87
	Months	92 (1) n=368	76 (2) n=368
ECOG-Performance Status (n=478)	1	98 (1) n=189	87 (2) n=189
	2	88 (2) n=201	64 (3) n=201
	3	63 (6) n=72	30 (5) n=72
	4	25 (11) n=16	6 (6) n=16
modified Glasgow Prognostic Score (n=478)	0	98 (1) n=178	91 (2) n=178
	1	87 (3) n=99	62 (5) n=99
	2	74 (3) n=201	46 (4) n=201
Lactate Dehydrogenase (U/L) (n=446)	<=250	95 (2) n=111	86 (3) n=111
	>250 U/L	83 (2) n=335	61 (3) n=335
Neutrophil Count (n=469) (n=469)	<=7.5 x 10^9/L	94 (1) n=321	93 (1) n=321
	>7.5 x 10^9/L	70 (4) n=148	70 (4) n=148

Where n<10, data not reported. SE= standard error.